Information Disclosure Statement

In compliance with 37 CFR 1.98(a)(2), Applicants submit herewith substitute copies of the references filed in the information disclosure statement of April 12, 2002. The Examiner is therefore requested to consider each of these references as set forth on the PTO Form 1449 submitted April 12, 2002. Applicants note that a substitute copy of reference "cab" will be submitted in due course.

Rejection of Claims 1-5 and 7-8 Under 35 U.S.C. § 112, Second Paragraph

I. Rejection of Claim 1 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 1 under 35 U.S.C. § 112, second paragraph for recitation of the phrase "effective amount." The Examiner states that "...the specification does not give the definition of effective amount." The Examiner also asserts that claim 1 is vague "[b]ecause there are many agent [sic] can be used to block the binding of lymphotoxin-β to its receptor," and requests that Applicants "point out which blocking agent is intended."

Applicants respectfully traverse the foregoing rejection on the grounds that claim 1 particularly points out and distinctly claims the subject matter, which Applicants regard as their invention, as, required by 35 U.S.C. § 112, second paragraph. Applicants submit that based on the plain language of the claim and the teachings in Applicant's specification, claim 1 is clear and definite to one of ordinary skill in the art.

Recitation of the term "effective amount" is art-recognized and is intended to mean an amount sufficient to effect beneficial or desired results as set forth in Applicants' claims, for example, such as treating viral-induced systemic shock or pulmonary distress. Applicants define the term "effective amount" at page 6, lines 9-10 of the specification. As described in the specification at page 6, lines 10-15, Applicants teach that an effective amount of an agent which blocks the binding of lymphotoxin-beta to its receptor is an amount of the agent that is sufficient to ameliorate, stabilize or delay the development of a viral response. Applicants also teach examples of how to determine the effective amount for administration, for example, at page 19, lines 15-22 of the specification. Applicants further teach that an effective amount can be

determined by performing *in vitro* receptor-ligand binding experiments. In view of the above, Applicants submit that the term "effective amount" is clear and definite.

With regard to the Examiner's assertion that claim 1 is vague with respect to the use of the phrase "agent which blocks the binding of lymphotoxin-β to its receptor", Applicants have amended claim 1 to specify that the agent is either a lymphotoxin-beta (LT-beta) blocking agent or a lymphotoxin-beta receptor (LT-beta-R) blocking agent as defined by Applicants. Specifically, Applicants teach that a LT-beta blocking agent is an agent which can diminish ligand binding to LT-beta, cell surface LT-beta clustering, or LT-beta signalling see e.g., page 4, lines 28-30 of the specification. As also described at page 4, line 30 to page 5, line 3, examples of LT-beta blocking agents include antibodies which bind to LT-beta and/or LT-alpha, soluble LT-beta-receptor/immunoglobulin (Ig) fusions, and antibodies to LT-beta receptor. Applicants also teach that a LT-beta-R blocking agent is any agent which can diminish ligand binding to LT-beta-R, cell surface LT-beta-R clustering, or LT-beta-R signalling at page 5, lines 4-6 of the specification. Examples of LT-beta-R blocking agents are also taught by Applicants, including soluble LT-beta-R/Ig fusion molecules and anti-LT-beta-R antibodies (page 5, lines 6-9 of the specification). Applicants submit that in view of the amendment to claim 1, this section 112, second paragraph rejection should be reconsidered and withdrawn.

II. Rejection of Claims 1-2, 4-5, and 7-8 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 1-2, 4-5, and 7-8 under 35 U.S.C. § 112, second paragraph for omitting essential steps, including "dosage of the agent, the rout of administration, and schedule of treatment." Claim 1 has been amended to specify a method of inducing an antiviral response in an individual suffering from viral-induced systemic shock and/or pulmonary distress, comprising administering to the individual an effective amount of a composition comprising a lymphotoxin-beta (LT-beta) blocking agent or a lymphotoxin-beta receptor (LT-beta-R) blocking agent, and a pharmaceutically acceptable carrier, such that an antiviral response is induced. Applicants submit that amended claim 1 completely defines the essential steps of

treating viral-induced systemic shock an individual using the claimed invention. In view of the amendment and the clear and definite description of the method of treatment provided in the specification, Applicants respectfully request that the Examiner withdraw this 112 rejection.

III. Rejection of Claim 2 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 2 as "vague and indefinite in that metes and bounds of 'an antibody' are not defined." Applicants respectfully traverse this rejection, and point out to the Examiner that previously pending claim 2 was not directed to an antibody. Claim 3, however, is directed to an antibody and has been amended to specify a method of inducing an antiviral response in an individual suffering from viral-induced systemic shock and/or pulmonary distress comprising administering a composition comprising an anti-LT-beta-R antibody, which binds LT-beta-R or soluble LT-beta-R. The term "anti-LT-beta receptor antibody" means any antibody, which binds to at least one epitope of the LT-beta receptor (page 5, lines 10-11 of the specification). Applicants teach examples of anti-LT-beta receptor antibodies, including chimeric and humanized, at page 10, lines 24-28 and at page 15, line 16 to page 17, line 27 of the specification. At page 11, line 9 to page 12, line 26 of the specification, Applicants also teach how to identify anti-LT-beta receptor antibodies. Applicants submit that the term "antibody" as used in claim 3 (and new claims 10, 11, 13, and 14) is clear and definite.

Accordingly, Applicants respectfully request that in view of the amendments to the claims and the reasons described above, the rejection under section 112, second paragraph be reconsidered and withdrawn.

Rejection of Claims 1-5 and 7-8 under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1-5 and 7-8 under 35 U.S.C. § 112, first paragraph. The Examiner states that the specification does not enable one of ordinary skill in the art to use "LT-β or LTβR-Ig for inducing an anti-viral response in human for other viruses, such as Sin

Nombre virus (SNV), Ebola virus, Marburg virus, Lassa virus, and Dengue virus." Applicants respectfully traverse this rejection.

The pending claims are directed to methods of inducing an antiviral response in an individual suffering from viral-induced systemic shock and/or pulmonary distress, comprising administering to the individual an effective amount of a composition comprising a lymphotoxin-beta (LT-beta) blocking agent or a lymphotoxin-beta receptor (LT-beta-R) blocking agent, and a pharmaceutically acceptable carrier, such that an antiviral response is induced. The claimed invention is also directed to a method of treating viral-induced systemic shock in an individual comprising administering to the individual an effective amount of a composition comprising a lymphotoxin-beta (LT-beta) or a lymphotoxin-beta receptor (LT-beta-R) blocking agent, and a pharmaceutically acceptable carrier, such that viral-induced systemic shock is treated. The pending claims also encompass a method of treating viral infection in an individual suffering from viral-induced systemic shock and/or pulmonary distress, comprising administering to the individual an effective amount of a composition comprising a lymphotoxin-beta (LT-beta) blocking agent or a lymphotoxin-beta receptor (LT-beta-R) blocking agent and a pharmaceutically acceptable carrier, such that treatment occurs. In one embodiment of the invention, the LT-beta blocking agent is an antibody against LT-beta or soluble LT-beta-R-Fc molecules. In another embodiment of the invention, the LT-beta-R blocking agent is an anti-LT-beta-R antibody which binds LT-beta-R or soluble LT-beta-R or an LT-beta-R/immunoglobulin fusion (Ig fusion) protein. The claimed method can be used to treat an individual who is infected with Sin Nombre Virus, Ebola virus, Marburg virus, Lassa virus or Dengue.

As amended, the claims are directed to methods of inducing an antiviral response and methods of treating viral infections comprising administering to an individual suffering from viral-induced systemic shock and/or pulmonary distress either a LT-beta blocking agent or a LT-beta-R blocking agent. LT-beta blocking agents and LT-beta-R blocking agents are both clearly defined in the instant specification at page 4, line 28 to page 5, line 9. Applicants also describe examples of LT-beta and LT-beta-R blocking agents, describe methods of identifying said

blocking agents, and provide working examples and data which support the claimed therapeutic use of LT-beta blocking agents or LT-beta-R blocking agents.

Applicants provide numerous examples of LT-beta blocking agents and LT-beta-R blocking agents in the instant specification, *e.g.* page 10, lines 18-23. Applicants disclose that soluble LT-beta-R molecules can be used as LT-beta-R blocking agents, wherein the extracellular portion of LT-beta-R competes with native LT-beta-R for ligand binding, see, *e.g.* page 12, line 27 to page 13, line 6, and teach fusion proteins comprising LT-beta-R and a heterologous domain, see *e.g.*, page 13, line 7 to page 15, line 15. Applicants also teach use of anti-LT-beta-R antibodies and provide examples, such as monoclonal, polyclonal, chimeric and humanized, see, *e.g.* page 15, line 16 to page 17, line 27.

As well as teaching examples of LT-beta blocking agents and LT-beta-R blocking agents, Applicants also teach screening assays for identifying said agents, for example, at page 10, line 24, to page 12, line 26 of the specification. Applicants teach that LT-beta blocking agents and LT-beta-R blocking agents can be identified using screening methods that detect the ability of the agent to bind to the LT-beta-R or LT-ligand. Alternatively, agents can be screened to determine if they are capable of inhibiting the effects of LT-beta-R signalling on cells.

In one example of a blocking agent screening method, Applicants disclose the tumor cell cytotoxicity assay which uses the cytotoxic effects of LT-beta-R signalling on tumor cells bearing LT-beta-R, wherein the tumor cells are exposed to activating agents which induce LT-beta-R signalling. Following activation, LT-beta blocking agents or LT-beta-R blocking agents are screened and identified based on their ability to inhibit the LT-beta-R activation. At page 11, lines 12-22 of the specification, Applicants provide a detailed example of a tumor cell screening assay, wherein tumor HT29 cells are cultured in wells for 3 to 4 days in the presence of a LT-beta-R activating agent, as well as in the presence or absence of the LT-beta-R blocking agent which is being identified. Vital dyes which measure mitochondrial function are added to the cells, which are then incubated. Finally, the optical density of each well is measured, and the number of tumor cells remaining is calculated. Based on this assay, Applicants teach that any

agent which reduces tumor cell cytotoxicity by 20% is considered an effective LT-beta-R blocking agent and thus can be used in the instant invention.

In addition to the tumor cell cytotoxicity assay, Applicants teach another method of selecting LT-beta blocking agents and LT-beta-R blocking agents involving measuring the agent's ability to interfere with LT ligand-receptor binding. At page 11, line 28 to page 12, line 26 of the specification, Applicants disclose numerous examples of such assays which can be used to identify LT-beta-R blocking agents. Applicants teach that blocking agents can be identified through ELISA or RIA assays, FACS analysis (which measures specific binding of the receptor and ligand), or through BIAcore TM technology, which allows the ligand-receptor dissociation constant and affinity constant to be directly measured. Applicants teach that each of these assays can be performed in the presence or absence of the blocking agent which is being studied for its ability to block LT-beta-R/ligand interactions.

Applicants submit that the instant specification fully enables one of ordinary skill in the art to treat viral-induced systemic shock and pulmonary distress as claimed. Applicants provide a working example of LT-beta and LT-beta-R blocking agents, wherein treatment of lymphocytic choriomeningitis virus (LCMV) infected mice with an LT-beta blocking agent prevents viral-induced acute response which is associated with LCMV infection (page 24, lines 24-27 and Figure 3 of the specification). ***Applicants use LCMV-infected mice as a model system for studying acute shock responses in individuals suffering from viral infections.*** Applicants demonstrate that survival is dramatically increased in LCMV-infected mice that are injected with a LT-beta-R blocking agent (a LT-beta receptor/Ig fusion) compared to control animals or those injected with an anti-TNF monoclonal antibody (see Figure 3). Specifically, Applicants demonstrate that LCMV-infected mice treated with the LTβR-Ig fusion protein have a 73% survival rate, compared to 20% of mice treated with either anti-TNFα antibody or TNFR55-Ig alone (page 24 and Figure 3). Furthermore, mice that survived due to the administration of a LT-beta-R blocking agent cleared the virus and did not show further signs of the disease (see page 26, lines 12-13).

Applicants submit that the data presented in the example section of the specification supports the claimed invention, and therapeutic uses thereof, and should not be used to limit the scope of the claimed invention. The LT-beta receptor/Ig fusion described in the working example is representative of the claimed LT-beta and LT-beta-R blocking agents described in the specification. The LCMV model system is representative of symptoms associated with viruses of the claimed invention. As noted by the Examiner, LCMV causes symptoms similar to SNV. Applicants support this statement in the specification at page 26, lines 1-3, where Applicants note that mice infected with a high dose of LCMV develop "an acute, rapidly progressive disease that shares several common traits with Ebola, Marburg, Lassa, Dengue, and Sin Nombre." ***LCMV is an accepted model for studying of virus-induced systemic shock and respiratory distress,*** including, but not limited to SNV. Thus, Applicants assert that examples of LT-beta and LT-beta-R blocking agents and the LCMV model system taught in the specification, should not be used to limit the claimed invention as suggested by the Examiner.

In contrast to the Examiner's assertion, Applicants teach that there are many commonalties among the group consisting of the Sin Nombre Virus, Ebola virus, Marburg virus, Lassa virus or Dengue. Applicants teach that pathology associated with each of these viruses may be immune mediated, and that each infection involves systemic distribution of infection, particularly targeting endothelial cells and macrophages (page 10, lines 8-9 and page 1, lines 14-18, respectively). Applicants also teach that inhibiting the LT system might increase an infected individual's chance for survival, by reducing virus specific CD8 T cell numbers and their functionality (page 10, lines 9-11).

The Examiner suggests that since Sin Nombre Virus, Ebola virus, Marburg virus, Lassa virus, and Dengue do not each share the same classification designation, each virus must operate through different mechanisms. Based on the teachings of the instant specification, the Examiner's reasoning is flawed. Applicants provide a working example in the specification using LCMV infected mice, wherein LCMV is a recognized model for studying viral-induced reactions, including those induced by SNV. SNV is a member of the Bunyviridae genus and

LCMV is a member of the Old World Arenaviridae genus (Fields, et al. Virology 3rd ed., page 1506, Table 1). Although LCMV and SNV are classified differently, LCMV shares common mechanisms with SNV such that LCMV is an accepted model system for studying virus/host interactions. Lassa virus is classified in the same genus as LCMV, the Old World Arenaviridae genus, and therefore, by the Examiner's reasoning, should be fully enabled in view of the example taught in the specification.

Applicants maintain that the specification fully enables one of ordinary skill in the art to make and use the claimed invention, and respectfully request that the Examiner withdraw the 112, first paragraph rejection.

Rejection of Claims 8-10 Under 35 U.S.C. §102

The Examiner has rejected claims 1-5 and 7-8 as being anticipated by Browning *et al.* (WO 98/17313, hereinafter '313) under 35 U.S.C. §102(a). The Examiner states that '313 teaches a "method for treating human immunodeficiency virus in mammal comprising the step of administering a pharmaceutical composition comprising therapeutic affective amount of LT-β–R blocking agent and a pharmaceutical acceptable carrier." Applicant respectfully traverses this rejection.

Amended claim 1 and dependent claims 3-5 and 7-8 are directed to a method of inducing an antiviral response in an individual suffering from viral-induced systemic shock and/or pulmonary distress, comprising administering to the individual an effective amount of a composition comprising a lymphotoxin-beta (LT-beta) blocking agent or a lymphotoxin-beta receptor (LT-beta-R) blocking agent, and a pharmaceutically acceptable carrier, such that an antiviral response is induced.

Applicants submit that reference '313 does not teach or suggest Applicants claimed invention. Reference '313 describes the use of LT blocking agents as a priming agent to be used ***in combination with other antiviral agents***, and ***does not describe the use of LT blocking agents for treating viruses directly***. The LT blocking agent described in '313 does not act

directly on the virus itself. Reference '313 describes how LT blocking agents can be used to release certain viruses that hide out on the surface of follicular dendritic cell (FDC) networks, such as HIV, by effectively collapsing the FDC networks. HIV is an example of such a virus in that it hides out on the surface of FDC networks. As such, collapsing the FDC networks by administering LT blocking agents releases the bound HIV and hence makes it susceptible for inhibition by known antiviral agents.

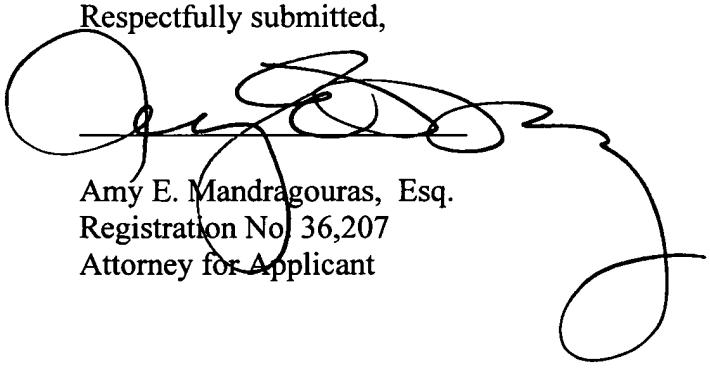
In contrast, Applicants have shown that LT blocking agents are effective in ***directly blocking severe host responses to aggressive viruses***, such as with Sin Nombre Virus, Ebola virus, Marburg virus, Lassa virus or Dengue. These viruses trigger excessive immune responses in the host that can be highly detrimental or lethal. The LT blocking agents act ***directly*** to reduce the hosts immune response to the virus, thus sparing the infected individual the severe consequences of an overactive immune system. Thus, unlike the '313 reference, it is not necessary to combine the LT blocking agent with a second antiviral agent. Furthermore, in contrast to reference '313, Applicants method of treatment is T-cell based and does not rely on liberating HIV from a FDC reservoir in order to affect humoral responses.

In addition, the amended claims relate to the treatment of viral infections in ***patients with systemic shock and/or pulmonary distress***, indications which result from infection with acute rapidly progressing diseases associated with viral infection, including infection with Ebola, Marburg, Lassa, Dengue, and Sin Nombre viruses. Applicants submit that HIV infection, described in the '313 reference, is not associated with systemic shock and/or pulmonary distress as required by the pending claims. Accordingly, Applicants respectfully request that the Examiner withdraw the §102 rejection of claims 1-5 and 7-8.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicant's Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

1. **(Amended)** A method of inducing an antiviral response in an individual suffering from viral-induced systemic shock and/or pulmonary distress, comprising administering to the individual an effective amount of a composition comprising ~~an~~ a lymphotoxin-beta (LT-beta) blocking agent or a lymphotoxin-beta receptor (LT-beta-R) blocking agent ~~which blocks the binding of lymphotoxin-β to its receptor~~, and a pharmaceutically acceptable carrier, such that an antiviral response is induced.

3. **(Amended)** The method of claim 1 ~~2~~, wherein said LT-beta blocking agent is an anti-LT-beta-R antibody which binds ~~against the~~ LT-beta-R ~~lymphotoxin-β □receptor~~ or ~~a~~ soluble LT-beta-R ~~lymphotoxin-β receptor~~.

4. **(Amended)** The method of claim 3 wherein said agent is a LT-beta-R/immunoglobulin fusion (Ig fusion) ~~lymphotoxin-β receptor/Ig fusion~~ protein.

5. **(Amended)** The method of claim 1 wherein said LT-beta blocking agent is a soluble lymphotoxin-~~β~~ beta or an antibody against lymphotoxin-beta ~~β~~.

7. **(Amended)** The method of claims 1-5 ~~1-6 5~~ wherein said individual is infected with Sin Nombre Virus, Ebola virus, Marburg virus, Lassa virus or Dengue.

8. **(Amended)** The method of claim 7 wherein the agent is a LT-beta-R ~~lymphotoxin-β-R~~/Ig fusion protein.